Chemical Genetic Approach to Production of hESC-derived Cardiomyocytes

Grant Award Details

Chemical Genetic Approach to Production of hESC-derived Cardiomyocytes

Grant Type: Comprehensive Grant

Grant Number: RC1-00132

Investigator:

Name:	Mark Mercola
Institution:	Sanford-Burnham Medical Research Institute
Type:	PI

Disease Focus: Heart Disease

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $2,832,000

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Grant Application Details

Application Title: Chemical Genetic Approach to Production of hESC-derived Cardiomyocytes

Public Abstract:

Adult heart muscle cells retain negligible proliferative capacity and this underlies the inability of the heart to replace muscle cells that are lost to injury, such as infarct, and underlies progression to heart failure. To date, no stem cell therapiy has produced significant cardiomyocyte replacement. Instead, transplanted cells, if they persist at all, produce endothelial cells or fibroblasts and the ameliorating effects on heart function that have been reported have been achieved by improving contractility, perfusion or other processes that are impaired in the failing heart. This proposal is to develop specific reagents and ultimately drugs to stimulate regeneration. Our approach integrates advances in stem cell biology, high-throughput (HT) biology, informatics and proteomics to identify small molecules, proteins and signal transduction pathways that control heart muscle formation from human embryonic stem cells (hESCs). High throughput assays will be developed and implemented to identify genes, signaling proteins, and small molecules that that control important steps in the differentiation, proliferation, and maturation of cardiac cells. Computer modeling and informatics will be used to identify and validate the signaling pathways that direct these critical processes. The discovery of small molecules and pathways will lead to protocols for 1) efficient directed differentiation of cardiomyogenic precursors from hESCs for research into transplantation and toxicology, 2) biotech reagents to stimulate cardiomyocyte renewal through directed differentiation of hESCs, and 3) cellular targets or lead compounds to develop drugs that stimulate regeneration from endogenous cells.

Statement of Benefit to California:

This proposal is a multidisciplinary collaboration among stem cell biologists, chemists, and engineers to address a critical problem that limits the widespread use of hESC for cardiology applications. Developing the multidisciplinary technology and overcoming the hurdles to application of hESCs to biotech and clinic will benefit California in many ways, including:

Research to discover novel tools to stimulate heart muscle regeneration from hESCs is clinically important. Cardiovascular disease is the single largest cause of death in the U.S. and the assays we will develop and the reagents themselves will be useful tools to direct cardiomyocyte regeneration. This will speed the translation of hESCs to the clinic, specifically by stimulating production of cardiomyocytes and potentially by enhancing their integration and function after engraftment.

Heart regeneration from hESCs probably uses similar cellular proteins and signaling pathways as regeneration of cardiomyocytes from other sources, thus, this research might be broadly applicable to heart muscle repair. Regeneration from endogenous cells remains controversial but these tools should be useful reagents to study and hopefully stimulate endogenous repair.

Bringing the diverse people together (chemists, cell biologists, and engineers) to address a stem cell problem forges new links in the academic community that should be capable of opening new areas of research. These new areas of research will be a important legacy of the stem cell initiative and promises to invigorate academic research.

The technology that we are developing applies the new discipline of chemical biology to stem cell biology, and the merger promises to spin off new areas of investigation and biotech products with the potential to benefit the practice of medicine and the local economy.

Lastly, supporting the leading edge technology and the collaboration will build the California infrastructure of high throughput chemical library screening so that it can be focused on other areas of biomedical research, both stem cell and non-stem cell.

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